Remarks

The above Amendments and these Remarks are in reply to the Office action mailed **May 17, 2000**. The undersigned attorney of record will address the Examiner's remarks in the order they were presented in the Office Action.

35 U.S.C §112, First Paragraph, Rejection

The Examiner has rejected claims 10-11 under §112, first paragraph, because in the Examiner's view Applicants do not teach how to use the claimed adenoviral compositions to provide gene therapy. To support the Examiner's position, the Examiner has cited *Orkin et al.* (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, distributed by the National Institutes of Health, Bethesda, MD or www.nih.gov, page 1). Further, the Examiner is also relying on the reference by *Verma, M. et al.* (Gene Therapy-promises, problems and prospects, Nature Vol. 389 page 239, paragraph #2). Applicants respectfully disagree with the Examiner's position, and thus traverse the rejection.

The Examiner's attention is drawn to pages 18-22 of Applicants' specification. There the Applicants describe, in detail, how the instant adenoviral vectors could be used to treat disease in a gene therapy context. The particular adenoviral vectors are described, as well as modes of administration, formulations, and viral doses. Applicants realize that these parameters may be varied when treating different patients affected by the same disease, but Applicants respectfully submit that a skilled practitioner of this art would know to vary the parameters to maximize patient benefit. In this regard, an analogy to

chemotherapy would be helpful in understanding why Applicants believe that claims 10 and 11 are enabled.

Chemotherapy is well established for treating cancer, yet, depending on the type of cancer, the degree to which it has progressed, and numerous other factors, including prior therapies, the patient's age and overall health, a skilled practitioner would expect to have to monitor the dose of a particular chemotherapeutic or try a variety of chemotherapeutic agents against a cancer that proves refractory. Applicants submit that gene therapy is no different. Clearly, one would not argue that the application of chemotherapy for cancer is not enabled because a skilled practitioner knows, and is expected to vary the parameters of treatment to effect maximum patient benefit. Applicants believe that this same standard should be applied to gene therapy, and thus respectfully submit that claims 10 and11 are enabled.

The Examiner has also stated that the specification lacks working examples, and has concluded that it would require undue experimentation to practice Applicants' invention, as it relates to claims 10 and 11. Applicants traverse the rejection for two reasons. First, Applicants have provided working examples, and the Examiner is referred to Examples 4 and 7. There, Applicants show the infection of cells with the claimed adenoviruses that can and do express cytosine deaminase and tumor necrosis factor, respectively. While these results were obtained in vitro, clearly a skilled practitioner of the art would have no difficulty extrapolating them to in vivo applications.

Second, to further support their position, Applicants are providing herewith two publications in the field of gene therapy to establish that a skilled practitioner of this art

does not have to engage in undue experimentation. Moreover, the papers show that gene therapy has become a predictable art, and in many respects is in the early phase of being practiced in a fashion analogous to chemotherapy.

The first publication is an abstract by *Nemunaitis, J. et al.*, "Adenoviral-mediated p53 gene transfer in sequence with cisplatin to tumors of patents with non-small cell lung cancer (NSCLC)," (1988) Cancer Gene Therapy, Vol. 5, pp. S32-S33. The second is a paper by *Cavazzana-Calvo, M. et al.* "Gene Therapy of Human Severe Combined Immunodeficiency (SCID)-X1 Disease," (2000, April) Science, Vol. 288, pp. 669-672. In the former publication, the authors show that adenovirus-mediated p53 gene therapy, in combination with cisplatinum, is effective, at least in a number of patients with non-small cell lung cancer. *Cavazzana-Calvo, M. et al.* describes the successful treatment using gene therapy of human immunodeficiency (SCID) disease in children. Thus, these references support Applicants' position that gene therapy has progressed to the point where it is a predictable therapy for treating cancer patients, and that one skilled in the art would not have to engage in undue experimentation to practice Applicants' invention as claimed in claims 10 and 11.

Claims 7-9 stand rejected under §112, first paragraph, because, in the Examiner's view, the specification does not enable one skilled in the art to make or use cells transfected as claimed in vivo. The Examiner is again referred to pages 17 and 18 of Applicants' specification. There, Applicants describe methods for administering the instant adenoviral compositions to infect the relevant target cells. Again, Applicants would like to draw the analogy to chemotherapy. There, a skilled practitioner knows that

not every patient will respond to a particular chemotherapeutic. What the practitioner knows full well, is that the therapy may have to be varied as to both the dose, and type of chemotherapeutic to maximize patient benefit. Applicants respectfully submit that a skilled practitioner of the art of gene therapy treats cancer patients similarly. That is, different patients may respond to different degrees with the same gene therapy treatment. Thus, the practitioner knows and expects that the parameters may have to be varied to maximize patient benefit. Thus, Applicants respectfully submit that claims 7 and 8 are enabled, and thus satisfy §112, first paragraph.

Finally, Applicants wish to remind the Examiner of the standard for enablement set forth in *In Re Marzocchi et al.*, (CCPA 1971) 439 Fed. 2nd, 169 USPQ 367. There the Court held that §112, first paragraph, requires nothing more than objective enablement. Applicants respectfully submit that their disclosure satisfies this standard, considering the level of detail in the specification and the level of knowledge of a skilled practitioner in the field.

35 U.S.C. §112, Second Paragraph, Rejections

Claim 1 stands rejected because Applicants have used the term "substantially." The Examiner will note that "substantially" has been deleted, and substituted therefor is the term "essentially."

Also regarding claim 1, the Examiner has rejected the claim based on the term "optionally." The Examiner will note that this term has been deleted.

Claims 5 and 12 have been rejected because of Applicants use of the phrase "vector that has the properties of a recombinant adenoviral vector consisting of." The

offensive language has been deleted. The Examiner will note that Applicants have deleted the plasmid vectors from claim 5, and they are now claimed in newly added claim 13.

35 U.S.C. §102 Rejections

Claims 1-4 and 7 stand rejected under §102(b) as being anticipated by *Hong et al.* (patent #5,643,567). For a claim to be rejected under a §102(b), the prior art reference must show each and every element of that which is claimed. Applicants respectfully submit that *Hung et al.* teach only a replication deficient recombinant adenoviral vector comprising a deletion in the E1B region that may be used to deliver either E1A or LT. *Hung et al.* do not show Applicants' instantly claimed vectors that permit the temporal expression of a heterologous gene in a pattern that essentially mimics the E1B gene it has replaced. Thus, on this basis alone, *Hung et al.* cannot be considered a proper §102(b) anticipatory reference.

Claims 1, 2, 4-9 and 12 stand rejected under §102(e) as being anticipated by *Gregory et al.* (patent #5,932,210).

Claim 4 is rejected because *Gregory et al.* show a total or partial deletion of the pIX gene located within the E1B region. The Examiner has referred the Applicants to the abstract of the patent. Similar to *Hung et al.* the Examiner will note that *Gregory et al.* do not show a feature of Applicants' claims; that is, the heterologous gene that is substituted for pIX exhibits a temporal expression pattern essentially similar to pIX. Thus, *Gregory et al.* cannot be considered to anticipate claim 4.

Claim 6 stands rejected because *Gregory et al.* describe a suicide gene in the abstract of the patent. Here too, Applicants note that *Gregory et al.* do not describe a

suicide gene that is expressed temporally in a pattern akin to the adenoviral gene that it is substituting for. Thus, Applicants submit that *Gregory et al.* do not anticipate claim 6.

Claims 5 and 12 stand rejected under *Gregory et al.* because the Examiner believes that this reference shows the construction of a replication competent recombinant adenovirus having the E1B region deleted, and inserted therefor a gene expressing cytosine deaminase which shares properties with Applicants' pΔE1B/CD. Specifically, the Examiner has referred the Applicants to column 13, lines 39-65 of the patent. Applicants respectfully submit that *Gregory et al.* do not show a replication competent, recombinant adenovirus. Rather, column 13, lines 39-65 provides a discussion of suicide genes and their uses, but no discussion of using them in the context of a replication competent recombinant adenovirus. Indeed, Applicants wish to note that on column 20, lines 59-62, *Gregory et al.* explicitly state that their vector "contains deletions in the E1A and E1B regions which render the virus replication deficient..." The Examiner is also referred to claim 1 of *Gregory et al.* which recites that "...all of the coding sequences of E1A, E1B and pIX, ...have been deleted." It is known in the art that the deletion of E1A and E1B provides a replication incompetent adenovirus. Thus, it should be apparent that the adenoviral vectors that *Gregory et al.* describe and claim are replication incompetent. Thus, since Applicants' vectors retain E1A it is respectfully submitted that the rejection of claims 5 and 12 should be withdrawn.

Claims 7-9 stand rejected under *Gregory et al.* Applicants respectfully traverse the rejection because *Gregory et al.* do not show host cells transformed with recombinant

adenoviral vectors that can express a heterologous gene with a temporal expression pattern essentially akin to the deleted E1B region gene it replaces.

The Examiner will note that Applicants have added claim 14. In view of the above Amendments and Remarks, reconsideration of claims 1-12 is requested, and consideration of newly added claims 13-14 is requested.

The Commissioner is authorized to charge any fees associated with this communication to Deposit Account No. 15-0615 for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

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